

found in Carey and Greene, and furthermore, the issue of protection groups is irrelevant to the compounds disclosed by Hattori and to the presently claimed compounds.

Carey and Greene are directed to hydroxyl-protection groups. As explained by Carey on page 678, "A common requirement in synthesis is that a hydroxyl group be masked as a derivative lacking an active hydrogen." In other words, in certain reactions, the hydrogen of a hydroxyl group can be quite active; Carey explains that "the acidic hydrogen of a hydroxyl group will destroy one equivalent of a strongly basic organometallic reagent and possibly adversely affect the reaction in other ways." *Id.* Thus, converting the hydroxyl group to another group with a less reactive hydrogen is a way of protecting the hydroxyl group during the reaction. After the reaction, the protection group is then replaced with the original hydroxyl group. As is evident from these references cited by the Office Action, each reaction type provides different factors that need to be taken into consideration when choosing an appropriate hydroxyl-protection group. No teaching is found in either of these references that all esters, alkyl groups, and ethers are equivalent hydroxyl-protection groups in all, most, or even some hydroxyl group-containing compounds and/or synthesis reactions involving these compounds.

Thus, the Office Action fails to establish by a finding of fact that esters, alkyl groups, and ethers are equivalent protection groups. Even if the Office Action could establish this, it has not established a reason or rationale for modifying the compound of Hattori. For example, neither Hattori nor the Applicants' disclosure refers to a problem requiring a protection group, or that their respective compounds are used in synthesis reactions, or provide any other reason why the R group should be protected. Thus, there is no showing why one of skill in the art would have substituted the R group of Hattori for a protection group.

Also, the Office Action asserts that one of skill in the art would have reasonably expected that altering R₁ of Hattori would result in phorbol derivative with a retained or even enhanced anti-HIV-1 capacity. This assertion is baseless and conclusory because it is not supported by any documentary evidence, nor is it supported by logic, sound scientific reasoning, or by established case law. The Office Action argues that just because some phorbol ester derivatives may have different faculties than those disclosed in Hattori, this does not necessarily mean that all differing phorbol derivatives would be ineffective against HIV-1. *See* page 3. In response, Applicants submit that a showing of a 0% chance of success is not necessary to show a lack of a reasonable expectation of success.

Furthermore, the Office Action still fails to produce any showing to meet its initial burden of establishing that one of skill in the art would of had a reasonable expectation of success. Thus, the burden has not shifted to the Applicants to prove that there would not have been a reasonable expectation of success. Nevertheless, Applicants have pointed to some teachings found in Hattori that indicate that one of skill in the art would not have had a reasonable expectation of success. The Office Action has failed to establish any findings of fact to counter Applicants' arguments or to otherwise meet its burden of establishing a reasonable expectation of success.

Therefore, the obviousness rejection is deficient in that it fails to establish by findings of fact: 1) that esters, alkyl groups, and ethers are equivalent protection groups; 2) that one of skill the art would have had a reason or rationale to modify the compound of Hattori as asserted by the Office Action; and 3) that one of skill in the art would have had a reasonable expectation that the asserted modifications would have successively resulted in phorbol derivatives with a retained, or even enhanced, anti-HIV-1 capacity.

Applicants also respectfully submit that the claimed compounds exhibit unexpected results over the compounds taught by Hattori, as evidenced by experimental data found in the

specification. The Table found on page 20 of the specification shows that four compounds according to the claimed invention (NPB-11 to 14) that were tested show biological stability in the blood, while compound N-6, corresponding to compound 6 of Hattori, was biologically unstable. Such results are unexpected over Hattori, because Hattori fails to discuss biological stability, let alone disclose any modifications that would have rendered its compounds biologically stable.

For at least these reasons, claims 1–3 and 5 would not have been rendered obvious by Hattori. Reconsideration and withdrawal of the rejection are respectfully requested.

B. Hattori and Raffanti

The Office Action rejects claims 7–14 under 35 U.S.C. §103(a) over Hattori in view of Raffanti and Haas (Goodman & Gilman's, The Pharmaceutical Basis of Therapeutics, 2001) ("Raffanti"). Applicants respectfully traverse the rejection.

For at least the reasons stated above, Hattori would not have rendered obvious claim 1. Raffanti, which is only applied by the Office Action to address the additional limitations recited in claims 7–14, fails to cure the deficiencies of Hattori with respect to claim 1. Therefore, the combination of Hattori and Raffanti would not have rendered obvious claim 1, or claims 7–14 that depend from claim 1. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

II. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of the application are earnestly solicited.

Should the Examiner believe that anything further would be desirable to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,



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